pyrazinamide, isoniazide, 6-mercaptopurine and 5-flurouracil may also result in pellagra like syndromes. Pyrazinamide and isonicotinic acid hydrazide (INH) are structural analogues of niacin and can depress endogenous niacin production by feedback inhibition or substrate competition. INH impairs the functioning of pyridoxine, a cofactor in tryptophan-niacin pathway and inhibits the niacin synthesis leading to pellagra.[2] Dermal pathogenesis reveals lowered collagen and urocanic acid content, serving as a filter for ultraviolet radiation, may cause photosensitive pellagra dermatitis. Chromatolytic changes are found in Betz cells of motor cortex. Similar cerebellar changes, optic neuropathy and cerebral deficit seen in pellagra encephalopathy may not resolve completely even with high doses of niacin. The diagnosis of pellagra is clinical. Laboratory diagnosis by fluorometric assay of urinary metabolites (2-pyridone/ N-methylniacinamide ratio less than 2.0) is not unequivocal evidence of pellagra. The recommended daily allowance is 10-20mg/day. Since niacin causes flushing, headache, burning and tingling sensations, niacinamide is prescribed orally (300-500 mg) and parenterally (100 mg per day) in divided doses. Neuropsychiatric manifestations are relieved dramatically overnight. Topically zinc oxide and para-aminobenzoic acid ointment may be advised.

Conclusion: Physicians should be aware of such cases and should treat any "sick" person with unexplained skin, neuro-psychiatric changes or gastrointestinal complaints with safe, inexpensive doses of niacin.

Acknowledgement: We are thankful to Prof PVS Rana, MD, DM (Neuro), Professor of Neurology, Manipal Teaching Hospital, Pokhara, Nepal, for his valuable guidance in preparing this manuscript.

RABINDRANATH DAS* *Associate Professor*[1]

SUDIP PARAJULI *Senior House Officer*[1]

SANJEEV GUPTA *Senior House Officer*[2]

Departments of Medicine[1&2] and Dermatology,[3] Manipal teaching hospital, Pokhara, Nepal.

das_rabindranath@hotmail.com

1. Mason JB. Lessons on nutrition of displaced people. *J Nutr* 2002: **132(7):** 2096S-2103S.
2. Jorgensen J. Pellagra probably due to pyrazinamide: development during combined chemotherapy of tuberculosis. *Int J Dermatol* 1983; **22(1):** 44-5.

Benign signet ring cells in the subserosa of the small intestine: a pseudoneoplastic phenomenon

Editor,

Aggregates of non-neoplastic signet ring cells have been previously described in the small intestine mucosa in ischaemia[1] and in association with Peutz-Jeghers polyps,[2] and in the colonic mucosa in ulcerated adenomas[3] and pseudomembranous colitis.[4] They are an uncommon finding that may be mistaken for signet ring cell carcinoma.

A similar phenomenon has also been identified outside the gastrointestinal tract.[5,6,7] We report a case in which non-neoplastic signet ring cells in the subserosa of the small intestine could potentially have been mistaken for signet ring cell carcinoma. As far as we are aware, benign signet ring cells mimicking signet ring cell carcinoma have never before been described in the subserosa of the intestine.

CASE REPORT A 76-year-old man presented with subacute bowel obstruction. Three years previously he had an extended right hemicolectomy for colonic adenocarcinoma. His past medical history included ischaemic heart disease and an abdominal aortic aneurysm. A barium enema showed a tight stricture, proximal to the point of previous anastamosis, suggestive of an obstructing tumour. He subsequently underwent laparotomy, resection of the strictured intestine and ileocolic anastamosis.

The surgical specimen consisted of 28cm of small intestine anastamosed to 3cm of large intestine. The distal small intestine was concentrically strictured adjacent to the point of anastamosis. Fibrinous exudate was present on the serosal surface and the small intestine wall was thickened. There was shallow mucosal ulceration in the strictured area.

Multiple sections were examined histologically. These showed features of an ischaemic stricture. There was mucosal ulceration and the submucosa was lined by inflamed granulation tissue. There was also fibrosis of the submucosa and subserosa. Where the mucosa was intact there was hyalinisation of the lamina propria. However, in several sections there was an abundance of cells with signet ring morphology localised to the subserosa (*Figure 1*). We were immediately concerned that these cells represented locally recurrent or metastatic signet ring cell carcinoma.

We reviewed the histology from the initial case. This was found to be an adenocarcinoma with an intestinal pattern and there was no signet ring differentiation. In addition we performed immunohistochemistry. The signet ring cells were negative for the epithelial markers CAM5.2 and AE1/AE3. We concluded that these cells were in fact not malignant and are a non-neoplastic mimicker of signet ring cell carcinoma.

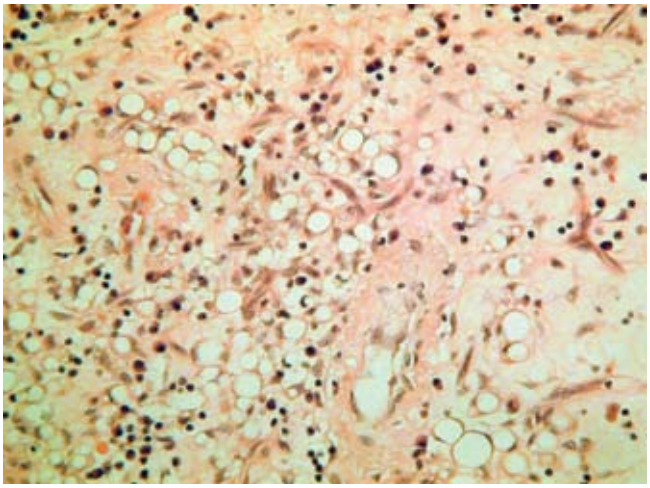

Fig 1A. Subserosal signet ring cells in groups and singly dispersed.

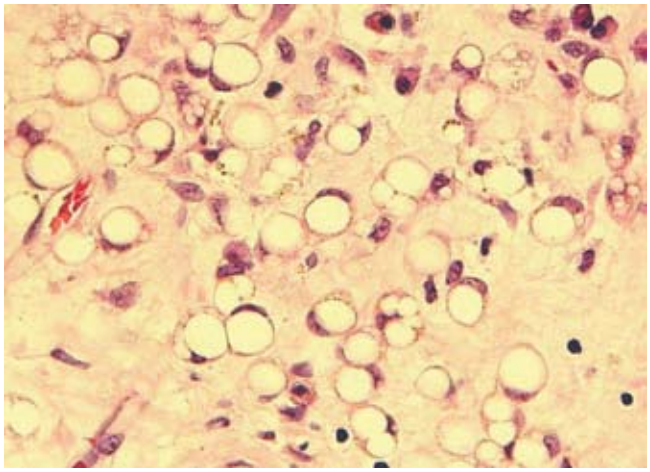

Fig 1B. High power view showing signet ring morphology.

DISCUSSION

Stricture of the small intestine can arise from a number of causes including ischaemia, carcinoma, lymphoma, Crohn's disease and tuberculosis.[8] This patient had a past history of vascular disease including myocardial infarction and an abdominal aortic aneurysm, and while histology of the small intestine showed features of an ischaemic stricture, the abundance of signet ring cells in the subserosa was alarming.

He had a previous colectomy for adenocarcinoma and we considered the possibility that these signet ring cells represented local recurrence. We reviewed the histology from this tumour and found it to have an intestinal pattern with no signet ring differentiation. In addition we thought that these cells could represent metastatic signet ring cell carcinoma from a distant primary site such as the stomach. However in view of the overall context of ischaemia the possibility of a non-neoplastic process was entertained. Negative staining with epithelial markers and awareness of previously described accounts of benign signet ring cells in the intestine and at other sites helped us make the diagnosis of a non-neoplastic mimicker of signet ring cell carcinoma.

Aggregates of benign signet ring cells in the intestinal mucosa have previously been documented and are characterised by cells that are cytologically similar to signet ring cell carcinoma.[9] Distinguishing signet ring cell carcinoma from these non-neoplastic signet ring cells is difficult using morphology alone as features of malignancy, such as cytological atypia, are often not marked in signet ring cell carcinoma.[9] The subserosal benign signet ring cells in this case are a similar diagnostic dilemma and in our opinion, could have been mistaken for signet ring cell carcinoma.

A wide panel of immunohistochemical markers was performed. We considered a mesothelial origin for these cells given the subserosal location but staining with calretinin, thrombomodulin and WT1 proved negative. The histiocytic marker CD68 was also negative. The cells were positive with S100. While S100 positivity is seen in wide variety of cell types, in view of the morphology of these cells and given their location in the subserosa, we feel that they are most likely adipocytes distorted by subserosal fibrosis that has occurred secondary to intestinal ischaemia.

In contrast, mucosal aggregates of benign signet ring cells are thought to be dispersed Goblet cells derived from multipotent stem cells in the crypt base following ischaemic injury.[1] These cells stain positive for neutral mucins[1] and they are also positive immunohistochemically with pan-cytokeratin.[1] The subserosal aggregates of signet ring cells in this case are negative for both neutral mucins and epithelial immunohistochemical markers.

In summary, the distinction of non-neoplastic signet ring cells from signet ring cell carcinoma is vital as the incorrect diagnosis of signet ring cell carcinoma has obvious prognostic and therapeutic implications. We have described a case in which aggregates of benign signet ring cells in the subserosa of the small intestine could have been mistaken for signet ring cell carcinoma. An erroneous diagnosis was avoided by consideration of this finding in the context of all the changes present, through awareness of the existence of benign mimickers of signet ring cell carcinoma, and by the use of immunohistochemistry.

CONFLICT OF INTEREST

The authors have no conflict of interest

OISIN HOUGHTON,* SHO in Pathology.

BRIAN HERRON, Consultant Histopathologist.

Department of Pathology, Royal Group of Hospitals Trust, Grosvenor Road, Belfast BT12 6BA.

oisinpiaras@hotmail.com

REFERENCES

1. Biedrzycki OJ, Arnaout A, Coppen MJ, Shephard NA. Lesson of the month. Isolated goblet cells in subacute ischaemic enteritis: mimicry of signet ring cell carcinoma. *Histopathology* 2005; **46(4):** 460-462.
2. Chen KTK. Benign signet-ring cell aggregates in Peutz-Jeghers polyps: a diagnostic pitfall. *Surg Pathol* 1989; **2:** 335-338.
3. Michal M, Chlumska A, Mukensnabl P. Signet-ring cell aggregates simulating carcinoma in colon and gall bladder mucosa. *Pathol Res Pract* 1998; **194(3):** 197-200.
4. Sidhu JS, Liu D. Signet-ring cell associated with pseudomembranous colitis. *Am J Surg Pathol* 2001; **25(4):** 542.
5. Kim H, Dorfman RF, Rappaport H. Signet ring cell lymphoma. A rare morphologic and functional expression of nodular (follicular) lymphoma. *Am J Surg Path* 1978; **2(2):** 119-132.
6. Mendelsohn G. Signet-cell-simulating microfollicular adenoma of the thyroid. *Am J Surg Path* 1984; **8(9):** 705-708.
7. Wang HL, Humphrey PA. Exaggerated signet-ring cell change in stromal nodule of prostate: a pseudoneoplastic proliferation. *Am J Surg Path* 2002; **26(8):** 1066-1070.
8. Day D, Jass JR, Price AB *et al*. Vascular disorders of the small intestine. In: Morson and Dawson's gastrointestinal pathology. 4th Edition. Oxford. Blackwell Science. 2003. 350-351.
9. Wang K, Weinrach D, Lal A Musunuri S, Ramirez J, Ozer O, Keh P, Rao MS. Signet-ring cell change versus signet–ring cell carcinoma: a comparative analysis. *Am J Surg Pathol* 2003; **27(11):** 1429-1433.